CLINICAL REVIEW

Application Type	NDA
Application Number	22-573
Priority or Standard	Standard
Submit Date	November 25, 2009
PDUFA Goal Date	September 24, 2010
Division / Office	Division of Reproductive and Urologic Products (DRUP) / Office of Drug Evaluation III (ODE III)
Reviewer Name	Gerald Willett M.D.
Review Completion Date	September 21, 2010
Established Name	Norethindrone (NE) and ethinyl estradiol (EE) chewable tablets and ferrous fumarate (FF) chewable tablets
Trade Name	Pending
Therapeutic Class	Combination oral contraceptive (COC)
Applicant	Warner Chilcott, LLC
Formulation	Oral tablets, chewable
Dosing Regimen - Cycle Days (dose)	Days 1-24 (0.025 mg EE / 0.8 mg NE) Days 25-28 (75 mg ferrous fumarate placebo)
Indication	For use by women to prevent pregnancy
Intended Population	Women of childbearing age

Table of Contents

Table of Tables

List of Abbreviations and Definitions

AE	Adverse event
ALT	Alanine aminotransferase
ASC-H	Atypical squamous cells but cannot exclude high-grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
AST	Aspartate aminotransferase
BMI	Body mass index
CI	Confidence interval
COC	Combination oral contraceptive
CRF	Case report form
DRUP	Division of Reproductive and Urologic Products
ECG	Electrocardiogram
EE	Ethinyl estradiol
EDC	Estimated date of conception
EOS	End of study
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GGT	Gamma glutamyltransferase
hCG	Human chorionic gonadotropin
Hct	Hematocrit
HDL	High-density lipoprotein
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HSIL	High-grade squamous intraepithelial lesion
IB	Intracyclic bleeding
ICH	International Conference on Harmonization
IND	Investigational New Drug (application)
IRB	Institutional review board
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
LDL	Low-density lipoprotein
LDH	Lactic dehydrogenase
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial infarction
MITT	Modified intent-to-treat
NDA	New Drug Application
NE	Norethindrone
ODE III	Office of Drug Evaluation III
PI	Pearl Index
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SHBG	Sex hormone-binding globulin
SOC	System organ class
Tmax	Time of maximum plasma concentration
VTE	Venous thromboembolism
WY	Women years

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended for norethindrone 0.8 mg and ethinyl estradiol 0.025 mg chewable tablets and ferrous fumarate chewable tablets for the Applicant's proposed indication of "for use by women to prevent pregnancy."

1.2 Risk Benefit Assessment

Contraception

The risk benefit assessment is favorable for the primary indication of contraception. There is no evidence in the safety database submitted in this NDA to suggest that the use of 0.025 mg EE / 0.8 mg NE by women will result in any new safety problem or will result in an increased incidence of any known combined oral contraceptive (COC)-related adverse event compared to similar COCs. There was one deep venous thrombosis (DVT) in the pivotal trial (Study PR-00207). The occurrence of 1-2 thromboembolic events in comparable size trials is not uncommon. The oral irritation study (PR-10107) did not show any significant irritative or abrasional findings in the oral cavity for this chewable tablet.

The contraceptive benefit of this product is comparable to that of other approved COCs.

Table A presents the key contraceptive efficacy results provided by the Applicant for 19 "during treatment" pregnancies. This reviewer identified one additional pregnancy not initially considered by the Applicant (they originally provided Pearl Index calculations for 18 pregnancies).

Table A: Contraceptive Efficacy Data from the Pivotal Phase 3 Study PR-00207 (Based on 19 Pregnancies that Occurred During Cycles 1 to 13 Including 7 Days after Treatment, in Subjects 18 to 35 Years of Age)

Study	Cycles *	Pregnancies	Pearl Index	95% CI	KMLT **
PR-00207	12,297	19	2.009	1.210, 3.135	1.997

CI = confidence interval
* = The number of cycles = those in which back-up contraception in not used
** = Kaplan Meier life table estimate of contraceptive failure rate at 364 days
Source: Amendment 0007 (Aug 3, 2010) - Table 1; page 7 of 62

Table B presents the key contraceptive efficacy results determined by the FDA biostatistician Dr. Dwyer.

Table B: Contraceptive Efficacy Data from the Pivotal Phase 3 Study PR-00207) (Based on 19 Pregnancies that Occurred During Cycles 1 to 13 Including 7 Days after Treatment, in Subjects 18 to 35 Years of Age)

Study	Cycles *	Pregnancies	Pearl Index	95% CI	KMLT **
PR-00207	12,297	19	2.01	1.21, 3.14	2.00

CI = confidence interval
* = The number of cycles = those in which back-up contraception in not used
** = Kaplan Meier life table estimate of contraceptive failure rate at 364 days
Source: Tables 3 and 4 of Dr. Dwyer's review.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for postmarketing risk evaluation or mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for postmarketing requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

In this review the term **0.025 mg EE / 0.8 mg NE** refers to the to-be-marked product (both active and placebo constituents) that is the subject of this review. 0.025 mg EE / 0.8 mg NE represents a new COC product in the U.S. in regard to utilizing a new dosing combination of EE and NE. This will be the first COC which combines 0.025 mg EE with 0.8 mg of NE. These doses, however, both fall within the range of already approved dosages in COCs containing these combination products. EE doses of 0.02 mg, 0.03 mg, 0.035 mg and 0.05 mg are present in combination with NE in approved products. In regard to NE, doses of 0.4 mg, 0.5 mg and 1.0 mg have been used in combination with EE in approved products.

Three proprietary names – (b) (4) have been submitted by the Applicant within the course of this review. None of these proposed proprietary names was found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). The product in the development phase was also known as WC3026.

2.2 Currently Available Treatments for Proposed Indication

Contraceptive methods for females include:

- Barrier methods (condom, diaphragm, cervical cap)
- COCs
- Progestin-only oral contraceptives
- Intrauterine devices (levonorgestrel-containing and copper-containing)
- Injectable contraceptives
- Contraceptive implants
- Contraceptive vaginal rings
- Surgical sterilization (tubal ligation, intratubal obstructive devices)

Approved COCs containing EE and NE include the following dose combinations:

21 active combination tablets (monophasic therapy) and 7 days placebo

- EE = 0.035 mg / NE = 0.4 mg
- EE = 0.035 mg / NE = 0.5 mg
- EE = 0.035 mg / NE = 1.0 mg
- EE = 0.05 mg / NE = 0.4 mg

21 active combination tablets (triphasic therapy) and 7 days placebo

- EE = 0.035 mg / NE = 0.5 mg x 5 days, EE = 0.035 mg / NE = 0.75 mg x 7 days, and EE = 0.035 mg / NE = 1.0 mg x 7 days

Warner Chilcott's EE/NE COC brand names include:

- Ovcon 35 (EE = 0.035 mg / NE = 0.4 mg x 21 days and 7 days placebo)
- Femcon FE (EE = 0.035 mg / NE = 0.4 mg x 21 days and 7 days placebo ferrous fumarate) [Note: this is the only approved chewable COC]
- Ovcon 50 (EE = 0.05 mg / NE = 1.0 mg x 21 days and 7 days placebo)

Warner Chilcott's EE/NETA (norethindrone acetate) COCs include:

- Estrostep Fe (EE = 0.02 mg / NETA = 1.0 mg x 5 days, EE = 0.03 mg / NETA = 1.0 mg x 7 days, EE = 0.035 mg / NETA = 1.0 mg x 9 days, and 7 days placebo ferrous fumarate)
- Loestrin 21 1.5/30 (EE = 0.03 mg / NETA = 1.5 mg x 21 days and 7 days placebo)
- Loestrin 21 1/20 (EE = 0.02 mg / NETA = 1.0 mg x 21 days and 7 days placebo)
- Loestrin FE 1.5/30 (EE = 0.03 mg / NETA = 1.5 mg x 21 days and 7 days placebo ferrous fumarate)
- Loestrin FE 1/20 (EE = 0.02 mg / NETA = 1.0 mg x 21 days and 7 days placebo ferrous fumarate)
- Loestrin 24 FE (EE = 0.02 mg / NETA = 1.0 mg x 24 days and 4 days placebo ferrous fumarate)

Approved combination oral contraceptives approved in the U.S. that are based on 24 active pills and 4 placebo tablets include:

- Loestrin 24 FE (EE = 0.02 mg / NETA = 1.0 mg x 24 days and 7 days placebo ferrous fumarate)
- Yaz (EE = 0.02 mg / Drospirenone, DRSP = 3.0 mg x 24 days and 4 days placebo)

2.3 Availability of Proposed Active Ingredients in the United States

Ethinyl estradiol is the most commonly used estrogen in combination oral contraceptives, with nearly 50 years of marketing experience.

Norethindrone has been studied since the early 1950s and has been marketed in COCs since the 1960s.

2.4 Important Safety Issues with Consideration to Related Drugs

COCs as a general class have a number of safety issues that have been well-recognized since their introduction in the 1960s. The following adverse events represent the major concerns described in contraceptive labeling:

- Vascular events, which may be fatal, including:
    - Deep venous thrombosis, pulmonary embolism, other venous thromboses
    - Myocardial infarction (especially in women >35 years who smoke)
    - Stroke (both ischemic and hemorrhagic types reported)
- Hepatic adenomas, hepatic nodular hyperplasia, cholestasis
- Blood pressure increase
- Gallbladder disease
- Headaches
- Irregular uterine bleeding, amenorrhea, oligomenorrhea
- Nausea
- Breast tenderness
- Mood changes
- Hypertriglyceridemia

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 76,629

The to-be-marketed product in this Application was developed under IND 76,629.

A pre-IND teleconference was held on February 15, 2007 for 0.025 mg EE / 0.8 mg NE. Pertinent recommendations included the following:

- As the proposed product will provide higher exposure to NE than the Femcon (0.8 mg compared to 0.4 mg) chewable product, an oral irritation study is requested.

- The Division requests a total of 10,000 28-day cycles of product exposure in the Phase 3 efficacy and safety trial, including 200 women who complete 13 cycles of use.

Medical Officer's Comment:
These recommendations were met by the Applicant.

A pre-NDA meeting was scheduled for June 23, 2009 but cancelled after the Applicant received the DRUP responses to their questions. One pertinent clinical comment expressed by the Division is the following:

- The description of pregnancies used in the calculation of the Pearl Index is not in accord with the Division's definition of "on drug" pregnancies: all conceptions that occur from Day 1 (the initiation of study drug) to seven days after the final tablet (i.e., the last placebo tablet) in the pill pack is taken. If the pills are stopped prior to completing a 28-day pill pack, "on drug" pregnancies are defined as conceptions from Day 1 to seven days after the final tablet is taken.

2.6 Other Relevant Background Information

All of the relevant background information was conveyed in the preceding sections.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant provided statements in their Pivotal Phase 3 Study PR-00207 that the study met all local legal and regulatory requirements. Protocols and protocol amendments were reviewed and approved by each of the study site's Independent Ethics Committee (IEC) or Institutional Review Board (IRB). The studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP).

The FDA's Department of Scientific Investigations (DSI) at the request of DRUP

investigated 2 clinical sites (Table 1). These sites were primarily chosen based on the number of subjects and the lack of recent inspections. There was no suspicion that there were sites suspicious for having data integrity problems or investigators with competing financial interests. The data from both sites was deemed acceptable by DSI with no evidence of discrepancies or regulatory violations in either site.

Table 1: Division of Scientific Investigations (DSI) Inspections for NDA 22-573

Study	Indication	Site number/ number enrolled	Investigator	Action
PR-00207	Contraception	205 / 46	Blumenau	No Action Indicated (NAI)
		246 / 51	Parker	No Action Indicated (NAI)

Source: DSI Consult Clinical Inspection Summary; July 27, 2010

3.2 Compliance with Good Clinical Practices

The Applicant provided statements in all of their clinical trials (Study protocols PR-00207, PR-10107, PR-00807, PR-00907, PR-03808 and PR-00707) that the studies were conducted in accordance with Good Clinical Practice (GCP).

The Applicant certified that the services of any person debarred under section 306(a) and (b) were not used in any capacity in the clinical trials

3.3 Financial Disclosures

All investigators who participated in Protocols PR-00807, PR-00907, PR-03808, PR-00707, PR-00207 and PR-10107 certified to not having a financial interest in these studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

In this Application, information regarding the active drug substances, NE and EE, was referenced to the respective manufacturers' Drug Master Files (DMFs) for which authorization letters from the DMF holders were provided. The respective DMFs were reviewed on found to be adequate.

The original NDA, supported by additional requested information submitted during the review, provided adequate information regarding the final drug product (NE/EE tablets and ferrous fumarate tablets) to support approval of the final drug

product. The primary Chemistry Reviewer (Jane Chang, PhD) made the following statements in her Summary of Chemistry Assessment:

> "*The specification for WC3026-5C [NE/EE] chewable tablets includes description, identification, uniformity of dosage unit, assay, degradation products, dissolution, assay of* (b) (4)*, and hardness. Except for the dissolution method for WC3026-5C chewable tablets, the proposed specification is acceptable to ensure product identity, strength, purity, and quality. The acceptance criteria for the tests are acceptable based on their developmental studies, and the analytical methods for the tests are adequately validated. Per the review dated August 31, 2010 by the Biopharm reviewer, Dr. S. Suarez, the dissolution method for NE/EE tablets is acceptable as interim. The sponsor agreed to develop a more discriminating dissolution method and to submit the results within a year of expedition of the request. Stability data based on three registration batches and two additional batches support the proposed expiration dating period, 36-month when stored at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F)."*
>
> '*The request for a categorical exclusion from the preparation of an environmental assessment (EA) under 21 CFR 25.31(b) is acceptable."*

Dr. Chang made the following statement in the Recommendation and Conclusion on Approvability section of her CMC Review signed on September 9, 2010:

> *"This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has made an "Acceptable" site recommendation. The labels have adequate information as required. Therefore, from the CMC perspective, this NDA is recommended for "Approval."*

No Phase 4 (Postmarketing) commitments were requested.

4.2 Clinical Microbiology

Microbiology review was not needed for this application because the product consists of oral tablets.

4.3 Preclinical Pharmacology/Toxicology

Dr. Krishan Raheja reviewed the nonclinical pharmacology and toxicology in NDA 22-573. His recommendation on approvability is the following:

"Pharmacology/toxicology recommends approval of NDA 022573 for contraception."

Dr. Raheja's overview of nonclinical findings stated:

"In lieu of nonclinical pharmacology and toxicology information on the active ingredients in (b) (4), norethindrone and ethinyl estradiol, the sponsor has made reference to Warner Chilcott's NDA 17-576 for Ovcon (norethindrone 1 mg and ethinyl estradiol 50 ug tablets, USP) which received FDA approval on August 28, 1975. Sponsor has stated that NDA 17-576 is annually updated with relevant published abstracts obtained from the nonclinical and clinical literature."

Dr. Raheja did not find any nonclinical safety issues relevant to clinical use.

4.4 Clinical Pharmacology

The clinical pharmacology review was performed by Dr. Christian Grimstein. His conclusions and recommendations are the following:

Absorption

Both NE and EE are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for NE and 43% for EE. Maximum plasma concentrations occur within 2 hours after oral administration. Following multiple-dose administration of NE/EE tablets, mean maximum concentrations of NE and EE were increased by 126% and 14%, respectively, as compared to single-dose administration. Mean NE and EE exposures (AUC values) were increased by 239% and 55% respectively, as compared to single-dose administration.

Food Effect

Single-dose administration of NE/EE tablets with food (1) decreased the Cmax of NE by 47% and but increased the AUC by 10-14% and (1) decreased the Cmax of EE by 39% but not AUC. In spite of the effect of food on the absorption of NE/EE tablets, the product may be administered with or without food because this was the instructions given to subjects in the applicant's single Phase 3 clinical trial.

Effects of Renal or Hepatic Impairment

The pharmacokinetics of NE/EE tablets have not been studied in subjects with renal impairment. The pharmacokinetics of NE/EE tablets have not been studied in subjects with hepatic impairment. Steroid hormones, however, may be poorly metabolized in patients with impaired liver function. Product labeling contraindicates the use of NE/EE tablets in women with liver tumors, benign or malignant, or liver disease.

Effects of Water after Chewing NE/EE Tablets

There was a small reduction on the Cmax for EE when NE/EE tablets were chewed and followed by 45 mL water compared to the Cmax when tablets were chewed and not followed by water. The mean AUC value for EE and the mean

Cmax and AUC values for NE, however, for tablets that were chewed followed by 45 mL water compared to the Cmax when tablets were chewed and not followed by water were within 80% - 125% of each other. Bases on these observations, the values for EE did not support bioequivalence (the lower bound for the difference for Cmax for EE was 76.5% instead of ≥ 80%) by the 2 dosing regimens, However, NE values Cmax and AUC supported bioequivalence. Based on these data, the Clinical Pharmacology Reviewer has recommended that labeling state that tablets are to be chewed without water.

Overall Assessment

The primary Clinical Pharmacology Reviewer, Christian Grimstein PhD, stated the following in his Review signed on September 1, 2010:

> *"NDA 022573 is acceptable from a Clinical Pharmacology perspective, provided an agreement can be reached with the sponsor pertaining to labeling language*."

Dr. Grimstein did not request any Phase 4 commitment.

4.5 Biostatistics

The primary Biostatistical Reviewer, Kate Dwyer PhD, stated the following in her Statistical Review, signed on September 17, 2010:

> The study results support the efficacy of WC3026 [NE/EE tablets], a 28-day low dose combination oral contraceptive (COC), in preventing pregnancy as demonstrated by the Pearl Index of 2.01 (95% Confidence Interval: 1.21 to 3.14).

Medical Officer's Comment:

Dr. Dwyer did a subgroup Pearl Index analysis of subjects with body mass index (BMI) ≥ 30 but ≤ 35 kg/m^2 (Subjects with BMI > 35 kg/m^2 were excluded per protocol). She found a slightly higher Pearl Index of 2.89 for subjects with BMI ≥ 30 kg/m^2, based on four pregnancies in this subgroup. The overall percentage of subjects with BMI ≥ 30 kg/m^2 in the entire treated population was 263/1677 = 15.6%. The percentage of pregnant subjects with BMI ≥ 30 kg/m^2 was 4/19 = 21.0%. These percentages are similar. It is difficult to conclude based on only 4 subjects that there is a definite efficacy correlation with BMI ≥ 30 but < 35 kg/m^2, particularly where one of the pregnant subjects had a BMI of 30.3 kg/m^2. A single pregnancy makes a large difference in the Pearl Index calculation.

The product labeling will reflect that the efficacy in women with a BMI > 35 kg/m^2 has not been studied.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Pivotal and supportive clinical studies are presented in tabular format in this section (Table 2 and Table 3). These include the contraception trial and the oral irritation study.

Table 2: Pivotal Phase 3 Study PR-00207 for Contraception

Protocol No. (Report No.) Start date Completion date Country (No. of study sites)	Study phase Study design Study duration	Treatment groups with dosing and duration	Number of subjects	Age range in years (mean) for MITT (N=1570) Ethnic origin for Treated subjects (N=1677)
PR-00207 (RR-03009) June/2007 January/2009 U.S. (69)	Phase 3 efficacy and safety Multicenter Open-label 13 cycles (28 days each)	To-be-marketed regimen: 24 days 0.025 EE / 0.8 mg NE 4 days ferrous fumarate	Treated = 1,677 MITT (ALL) = 1,570 MITT (18-35 years) = 1,251 MITT (> 35 years) = 319 MITT (who completed at least 360 days of treatment) = 746	18-46 (28.8) Asian 30 (1.8%) Black 228 (13.6%) Caucasian 1182 (70.5%) Hispanic 199 (11.9%) Native American 8 (0.5%) Other 30 (1.8%)

EE = ethinyl estradiol; NE = norethindrone; MITT = modified intent to treat
MITT was defined as the subset of all treated subjects who were evaluated for pregnancy, either positive or negative, at least once after beginning study medication
Source: NDA 22-573; Section 5.2, Tabular listing of all clinical studies; page 2 of 2.

Table 3: Phase 1 Supportive Safety Study PR-10107

Report No. (Protocol No.) Start date/ Completion date Country (No. of study sites)	Study phase Study design Study duration	Treatment group	Subjects	Age range in years (mean) Race
PR-10107 / RR-00309 Oct/2008 Dec/2008 U.S. (1)	Phase 1 safety Single-center Open-label Uncontrolled 24 days	24 days 0.025 EE / 0.8 mg NE	Enrolled = 54 Completed study = 52	19-46 (35.2) Black = 10 (18.5%) Caucasian = 44 (81.5%)

EE = ethinyl estradiol; NE = norethindrone
Source: NDA 22-573; Section 5.2, Tabular listing of all clinical studies; page 2 of 2.

5.2 Review Strategy

Sections 5.3.1 and 5.3.2 contain detailed information about the pivotal contraceptive safety and efficacy study and the supportive safety study.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Pivotal Study PR-00207 (Report RR-03009) for Contraception

5.3.1.1 Study Title / Study Dates

"An Open Label Study of the Contraceptive Efficacy of an Extended Regimen of Norethindrone and Ethinyl Estradiol, Study PR-00207"

This study ran from June 21, 2007 until January 23, 2009

5.3.1.2 Ethics

The Applicant stated that:

- The protocol, protocol amendments, and informed consent documents were reviewed and approved by an Investigational Review Board (IRB) in accordance with the provisions of 21 CFR Part 56.
- The study was carried out in accordance with Good Clinical Practice

(GCP) and the United States (US) Code of Federal Regulations, Title 21. These standards respect the following guidelines: International Conference on Harmonization (ICH) Harmonized Tripartite Guideline, the Guideline for Good Clinical Practice, and the Declaration of Helsinki and amendments.

5.3.1.3 Study Sites

In Study PR-00207, 69 study sites screened and randomized subjects

Medical Officer's Comment:
Clarification was sought from the Applicant because the number of study sites was listed as 70 in one section of the study report and 68 in another. The Applicant stated that 69 sites screened and randomized subjects in an amendment response to an information request. This number of sites (69) was also verified in the datasets by this reviewer.

5.3.1.4 Study Objectives

The primary objective of the study was to assess the efficacy of 0.025 mg EE / 0.8 mg NE in the prevention of pregnancy.

The secondary objectives were to assess the incidence of intracyclic bleeding (IB) and to assess the safety and tolerability of the product.

5.3.1.5 Study Design

Study PR-00207 was designed as a multicenter, open-label, uncontrolled clinical trial. The trial was designed to run for 13 cycles (28 days per cycle). The drugs and drug dosages for each cycle are shown in Table 4:

Table 4: Study PR-00207 – Dosages for 0.025 mg EE / 0.8 mg NE throughout the 28-Day Cycle

Cycle Days	No. of oral intake days	Content
1-24	24	24 green colored tablets (0.025 mg EE / 0.8 mg NE), one tablet orally per day
24-28	4	4 lilac colored ferrous fumarate tablets (placebo), one tablet orally per day

Source: Study Report RR-03009; page 22 of 297

The study plan called for 1,600 heterosexually active women aged 18 to 45 and at risk of becoming pregnant to be enrolled (1,700 were actually enrolled). The pregnancy rate was to be assessed in terms of the Pearl Index and by life table methods.

All pregnancies occurring during the study and within 30 days after the end of treatment were assessed to determine their relationship to the use of the products in this study. Pregnancies found to have an estimated date of conception within 7 days after the last study treatment were to be counted as "during treatment" pregnancies.

Each subject was to be instructed to keep a daily record of her bleeding occurrences in a diary. Bleeding/spotting frequencies and patterns were to be evaluated.

The test product was to be taken by chewing one tablet at approximately the same time each day without water; however, tablets could be taken with or without food.

For subjects who were switching to the test product from another hormonal contraceptive product, Day 1 of treatment was to be the day they would have started on the next cycle with their previous drug.

For subjects not using hormonal contraception who were starting the test product, the first day of menstrual flow was to be Day 1.

Medical Officer's Comment:

(b) (4)

. The labeling will be revised to reflect the clinical trial procedure.

<u>Instructions for Missed Pills (note: active tablets are green, ferrous fumarate placebo tablets are lilac)</u>

The following instructions were provided to the subjects:

If you MISS 1 green active pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.

2. You do not need to use a back-up birth control method if you have sex.

If you MISS 2 green "active" pills in a row in WEEK 1 OR WEEK 2 of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.

2. Then take 1 pill a day until you finish the pack.

3. You COULD GET PREGNANT if you have sex in the 7 days after you

miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method of birth control until you have taken a green "active" pill every day for 7 days.

If you MISS 2 or MORE green "active" pills in a row in WEEK 3 OR WEEK 4:

1. Start a new pack that same day.

2. You may not have your period this month, but this is expected. However, you should use the home pregnancy test to make sure you are not pregnant. If you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.

3. You COULD GET PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method of birth control until you have taken a green "active" pill every day for 7 days.

If you forget any of the 4 lilac pills (placebo) in week 4, keep taking 1 pill each day until the pack is empty. You do not need to use a back-up method of birth control.

Instructions for Vomiting, Diarrhea and Use of Certain Medicines

The instruction for these categories is the following:

IF YOU HAVE VOMITING (within 3 to 4 hours after you take your pill), you should follow the instructions for WHAT TO DO IF YOU MISS PILLS. IF YOU HAVE DIARRHEA or IF YOU TAKE CERTAIN MEDICINES, including some antibiotics, or the herbal supplement St. John's Wort, your pills may not work as well. Use a back-up method of birth control (such as condoms or spermicide) until you check with your healthcare provider.

Subjects could have been withdrawn from the study at the discretion of the investigator or sponsor due to poor compliance with protocol requirements.

5.3.1.6 Inclusion Criteria

For inclusion into the trial, subjects were required to fulfill all of the following criteria:

1. Age ≥ 18 and ≤ 45 years of age.

2. Negative serum pregnancy test.

3. Regular cycles with a usual length of 21-35 days and a variability of +/– 3 days; (subjects who are recently postpartum or post-abortion must have had at least 2 regular cycles).

4. Body mass index ≤ 35.0 kg/m^2.

5. Willing to use the study drug as the only method of contraception.

6. Signed an informed consent form.

5.3.1.7 Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the trial:

1. Was using hormonal contraception via the following routes and during the specified timeframes: hormonal implants and injectables within 9 months of study start; intrauterine contraception within 3 months of study start (women currently on oral, intravaginal or transdermal COC could be switched directly to study medication)

2. Was currently taking the herbal supplement, St. John's Wort
3. Had an abnormal Pap test result suggestive of low-grade squamous intraepithelial lesion (LGSIL) or worse. Enrollment of subjects with a Pap smear interpretation of "atypical squamous cells of undetermined significance but cannot exclude high-grade squamous intraepithelial lesion" (ASC-H) was not allowed. However, enrollment of subjects with an interpretation of "atypical squamous cells of undetermined significance" (ASC-US) was permitted, if human papilloma virus (HPV) reflex test result was negative

4. Was currently nursing

5. Had an untreated chlamydia infection

6. Had any disease or condition that compromised the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication

7. Had a known or suspected premalignant or malignant disease (excluding successfully treated skin cancers) or a history of steroid-dependent malignancy, including malignant melanoma

8. Had severe systemic disease, which might have interfered with the conduct of the study or the interpretation of the results

9. Had any abnormal findings or condition on the medical history, screening, physical/gynecological exam including abnormal baseline laboratory values that were considered clinically significant

10. Had a history of any of the following manifestations of cardiovascular disease: myocardial infarction, coronary artery bypass graft surgery, percutaneous angioplasty, or more than 50% angiographic narrowing of a coronary artery

11. Had congestive heart failure

12. Had uncontrolled hypertension; sitting systolic blood pressure (BP) ≥ 160 mmHg or diastolic ≥ 95 mmHg

13. Had a history of stroke or transient ischemic attacks

14. Had thrombophlebitis or thromboembolic disorder or a history of these conditions or known or suspected genetic component

15. Undergoing treatment with anticoagulants (heparin or warfarin)

16. Had uncontrolled thyroid disorders
17. Had a history of cholestatic jaundice associated with pregnancy or estrogen use, severe pruritus, or deterioration of otosclerosis

18. Had insulin-dependent diabetes mellitus

19. Had porphyria

20. Had experienced an increased frequency or severity of headaches including migraines during previous estrogen therapy

21. Had a history of drug addiction or alcohol abuse (within the last 2 years)

22. Currently suffered from depression or had a significant past history of depression

23. Had participated in another clinical trial within the previous month or if the subject had received an investigational drug within the last 3 months prior to study entry. Subjects who had participated in a clinical trial of oral contraceptives containing FDA approved active ingredients could be enrolled 2 cycles after completing the preceding study

24. Smoked > 15 cigarettes/day if > 35 years of age

25. In the opinion of the investigator were unable to fully comply with the study requirements

26. Had a known hypersensitivity to estrogen and /or progestins

5.3.1.8 Study Procedures

The study procedures for pivotal Study PR-00207 are found in Table 5.

Table 5: Study PR-00207 – Study Procedures

Assessment	S	Q	Interim Visits						FV	FU
Visit number	V1	V1A	V2	V3	V4	V5	V6	V7	V8	
Day		1	28	84	140	196	252	308	364	378-392
Cycle			1	3	5	9	7	11	13	
Informed consent	X									
Demographic data	X									
Entry criteria	X									
Gynecologic, medical, surgical and medication history	X								X	
Physical exam	X								X	
Pap test	X								X	
Chlamydia	X									
Blood pressure, heart rate	X		X	X	X	X	X	X	X	
Height	X									
Weight	X								X	
Pregnancy test	SE UR	UR	UR	UR	UR	UR	UR	UR	SE UR	
Chemistry, hematology and urinalysis	X								X	
Qualification		X								
Medication, diary cards and home pregnancy tests dispensed		X	X	X	X	X	X	X		
Diary cards and medication returned			X	X	x	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	
Compliance assessment			X	X	X	X	X	X	X	
End of study evaluation									X	
Questionnaire follow-up										X

Abbreviations: V = visit; S = screening; Q= qualification; FU = follow-up; SE = serum; UR = urine
Source: Study report RR-03009; page 26 of 297

Medical Officer's Comments:

- ***During the follow-up period, subjects were contacted or seen within 2-4 weeks after the end of treatment to determine if they had a withdrawal bleed and if any ongoing adverse events had resolved. If they had not had a withdrawal bleed, a pregnancy test was to be performed.***

5.3.1.9 Primary Efficacy Variable

The primary efficacy analysis was based on the Pearl Index in the group of women 35 years of age or less based on all at risk cycles where no other method of birth control is used. The Pearl Index for all subjects, regardless of age was also determined. The 95% confidence intervals for the Pearl Indices and life table estimates were also computed.

In this study the Pearl Index (PI) was computed as:

> PI = [1300 x number of pregnancies] divided by the number of woman-cycles of treatment.

5.3.1.10 Secondary Variables

The secondary target variables were the descriptive parameters of bleeding/spotting, safety and tolerability. The results of these analyses will be presented in the safety section. The definitions for bleeding patterns will be presented here.

Bleeding/Spotting

The following definitions were employed to analyze bleeding/spotting in Study PR-00207

Term	Definition
Spotting	Bleeding that is described as light and requiring no more than the use of a panty liner
Bleeding intensity = none	No vaginal bleeding
Bleeding intensity = light	Less than associated with normal menstruation relative to the subject's experience
Bleeding intensity = normal	Like normal menstruation relative to the subject's experience
Bleeding intensity = heavy	More than normal menstruation relative to the subject's experience
Bleeding (spotting) day	A diary day in which the subject reported bleeding (spotting)
Bleeding (spotting) episode	A set of consecutive bleeding (spotting) days preceded and followed by at least 2 bleed/spot free diary days. One or more single isolated bleed/spot free days may be included in a single episode. An episode will be considered a bleeding episode if it includes at least one bleeding day.
Withdrawal bleeding episode	The first bleeding episode (1) starting after the last day of active drug intake during a treatment cycle and before the beginning of the next treatment cycle, or (2) starting within 4 days of the last day of active drug intake during the treatment cycle and continuing at least through the first day after the end of active drug intake in the treatment cycle.
Intracyclic bleeding (IB) or spotting) day	Any bleeding or spotting day not included in a withdrawal bleeding episode
Intracyclic bleeding (IB) or spotting episode	A bleeding episode composed of intracyclic bleeding or spotting days.

The 13-cycle study period was divided for the purpose of bleeding analysis into 4 reference periods of 3 treatment cycles each. The first treatment cycle was not counted, so the first reference period started on the first day of study medication of Cycle 2. The onset day of an intracyclic bleeding episode is counted from Day 1 of the treatment cycle. The onset day of a withdrawal bleeding episode is counted from the last day of the treatment cycle (Day 0 of withdrawal).

Medical Officer's Comment:
Although the Applicant stated that they would not count the first treatment cycle they provided information on bleeding/spotting in the first cycle as well as each cycle. This is reflected later in the review when bleeding/spotting is discussed in relation to each individual cycle.

The following parameters of bleeding were calculated for each study subject, by cycle and overall:

- Incidence of withdrawal bleeding (yes/no)
- Median onset day of withdrawal bleeding
- Median duration of withdrawal bleeding
- Median intensity of withdrawal bleeding
- Incidence of IB (yes/no)
- Number of IB episodes
- Number of bleeding episodes
- Number of spotting-only episodes
- Maximum duration of IB episodes
- Maximum duration of bleeding episodes
- Maximum duration of spotting-only episodes
- Maximum intensity of IB episodes
- Maximum intensity of bleeding episodes
- Number of IB days
- Number of bleeding days
- Number of spotting-only days
- Total number of bleeding days including withdrawal bleeding and intracyclic bleeding

5.3.1.11 Statistical Analysis Plan

Population definitions

The all qualified population will include all subjects qualified to receive treatment in the study.

The all treated population was defined as all subjects who received treatment (at least one tablet).

The modified intent-to-treat (MITT) population was defined as those subjects who received treatment and who were evaluated for pregnancy, either positive or negative, at least once after beginning the study treatment.

The completed population was defined as those MITT subjects who completed at least 360 days of treatment based on diary reports.

Imputation

In the analysis of intracyclic bleeding (IB), single missing diary days were imputed using the maximum of the bleeding intensities of the day before and the day after the missing day. No imputations were made for 2 or more consecutive missing diary days: these days were considered as non-evaluable. A cycle with fewer than 14 evaluable diary days was excluded from the analysis by cycle. A reference period (each with 3 treatment cycles – beginning with cycle 2) with fewer than 56 evaluable diary days was excluded from the analysis by reference period.

5.3.1.12 Analysis of Safety

The safety monitoring employed in this protocol included medical history, physical exams, vital signs monitoring, safety labs, pap smears, bleeding pattern assessment and adverse event reporting. The MedDRA coding dictionary was used to assign preferred terms to adverse events.

The Applicant listed specific adverse events that could lead to withdrawal of the subject from the trial.

- Occurrence for the first time of migraine headaches or more frequent occurrence of unusually severe headaches
- Sudden perceptual disorders (e.g., disturbances of vision or hearing)
- First signs of thrombophlebitis or thromboembolic symptoms (for example, unusual pains in or swelling of the legs, stabbing pains on breathing or coughing for no apparent reason)
- Prolonged immobilization (for instance, following an accident or surgery) or 4 weeks before planned immobilization and surgery
- Onset of jaundice
- Onset of hepatitis
- Generalized pruritus
- Increase in epileptic seizures
- Significant (in the investigator's judgment) rise in blood pressure

Medical Officer's Comment:
This list provides examples of discontinuation reasons but was not intended to be all-inclusive.

5.3.1.13 Protocol Amendments

There were no protocol amendments.

5.3.1.14 Disposition of Subjects

Subject disposition in Study PR-00207 is presented in Table 6.

Table 6: Study PR-00207 – Overall Subject Disposition

Disposition / Reason	0.025 mg EE / 0.8 mg NE
Screened	2321 (100%)
Subjects not qualified for enrollment	621 of 2321 (26.8%)
• Screen failure	• 416 of 2321 (17.9%)
• Changed mind	• 86 of 2321 (3.7%)
• Could not comply	• 15 of 2321 (0.6%)
• Spouse/partner refusal	• 2 of 2321 (0.1%)
• Other	• 102 of 2321 (4.4%)
Subjects enrolled in the study	1700 of 2321 (73.2%)
Subjects enrolled but did not receive medication	23 of 2321 (0.9%)
Subjects receiving study medication	1677
MITT population	1570 of 1677 (93.6%)
• Age 18-35 years	• 1251 of 1570 (79.7%)
• Age > 35 years	• 319 of 1570 (20.3%)
Evaluable for IB assessment for cycles 2-13	1425 of 1677 (85.0%)
Subjects prematurely discontinuing study	686 of 1677 (40.9%)
• Loss to follow-up	• 271 of 1677 (16.2%)
• Withdrew consent	• 149 of 1677 (8.9%)
• Adverse events	• 143 of 1677 (8.5%)
• Protocol violation	• 25 of 1677 (1.5%)
• Pregnancy	• 23 of 1677 (1.4%)
• Death	• 0
• Other reasons	• 75 of 1677 (4.5%)
Completed subjects (MITT subjects finishing 360 days of treatment)	746 of 1677 (44.5%)

EE/NE = ethinyl estradiol / norethindrone; MITT = modified intent-to-treat (subjects who had at least one pregnancy test performed after starting treatment)
IB = Intracyclic bleeding (evaluable cycles had at least 14 evaluable diary days)
Source: Study Report RR-03009; Table 4, page 39 of 297; Figure 1, page 41 of 297; Table 14.1.1, page 103 of 297

Medical Officer's Comment:
Most of the subjects who did not qualify for enrollment and who were listed in the "other" category (102 of 2321 screened subjects) were listed as lost to follow-up (57 of 102). The second most common reason for being in the "other" category included not meeting deadline/closed enrollment (28 of 102).

The "other reasons" for subjects who prematurely discontinued could be identified in the EOS dataset. Among 75 treated subjects with "other reasons," listed for premature termination the three most common reasons were noncompliance (23), investigator site closure (illness of the investigator)(20) and subjects moving from the area (8).

5.3.1.15 Protocol Deviations

Of the 1,677 treated subjects in Study PR-00207, there were 25 protocol deviations leading to subject withdrawal. Of these withdrawals 22 of the 25 were in the MITT population. The reasons for the withdrawals in the MITT population included noncompliance (16), positive HPV test at enrollment (2), irregular periods (1), BMI > 35 at enrollment (1), "out of window" (1) and history of melanoma (1).

Medical Officer's Comment:
The Applicant did not initially provide overall information on protocol deviations for those who remained in the study. They provided this information after the Division's request with their Aug 3, 2010 submission. The majority of the protocol deviations were related to out of window visits. The remainder of the deviations were reviewed and not found to be significant in terms of the efficacy analysis.

5.3.1.16 Demographics

Demographic data for the MITT population in Study PR-00207 is found in Table 7.

Table 7: Study PR-00207 – Demographics and Baseline Characteristics - MITT

Parameter	(N=1570)
Mean age (years ± SD)	28.8 ± 7.1
Age range (years)	18-46
Ethnic group (%)	
• Caucasian	1131 (72.0%)
• Black	204 (13.0%)
• Hispanic	176 (11.2%)
• Asian	28 (1.8%)
• Native American	7 (0.4%)
• Other	24 (1.5%)
Switchers	819 (52.2%)
New users (non-switchers – see comment below)	751 (47.8%)
Current smokers	249 (15.9%)
Mean weight (lbs ± SD)	148.9 ± 29.1 lb
Weight range	74-243 lb

SD = standard deviation
Source: Study Report RR-03009 page 44 of 297

Medical Officer's Comment:
The Applicant was asked to clarify the term "new user" in an information request. In the Aug 3, 2010 response to a DRUP information request, the Applicant stated that all subjects who were not considered to be immediate switchers were considered as new users. Switchers were subjects who had been using combination hormonal contraception (oral, vaginal or patch) immediately prior to starting study drug. The number of first time users of a COC was not reported in this study.

The BMI for the subjects in the MITT population was obtained from dataset ADOPS. The mean BMI was 25.0 kg/m^2 ± 4.4 SD.
The BMI range was 14.9 – 35.9 kg/m^2.

5.3.1.17 Concomitant Medications

The most frequently recorded concomitant medications were sex hormones and modulators of the genital system (54.0%); in almost all cases this represented other COCs taken immediately before and/or after treatment with the study drug. Other classes of medication used by more than 10% of the subjects included: analgesics (30.8%), anti-inflammatory and anti-rheumatic products (28.8%), antibacterials for systemic use (27.4%), vitamins (20.8%), antihistamines for systemic use (17.7%), gynecological anti-infectives and antiseptics (13.1%), cough and cold preparations (12.0%), and psychoanaleptics (11.7%).

Medical Officer's Comment:
On analysis of the subjects using hormonal medications, this reviewer found that Subject 209/042 took Plan B during the study but that particular cycle was not excluded from the efficacy analysis. The Applicant was asked to provide a full evaluation of all women taking hormonal medications concomitantly with study drug during the study. They listed 179 cycles that were appropriately excluded from the efficacy analysis. The single cycle for Subject 209/042 was erroneously not excluded. Because there was only one cycle in this category the Applicant did not recalculate the Pearl Index. This reviewer agrees that recalculation for a single cycle is not necessary and would not impact the Pearl Index calculation.

5.3.1.18 Primary Efficacy Results– Pregnancies

During Treatment Pregnancies

The "during treatment" pregnancies are shown in Table 8.

Table 8: Study PR-00207 – Pregnancies during Study Treatment (Includes Pregnancies with Estimated Date of Conception within 7 Days after Last Pill Intake

Site	Subj. # (age) [BMI kg/m^2]	Treatment start	Treatment end	EDC	Notes
Age 18 to 35 - Within 13 Cycles – EDC while on treatment					
200 (1)	034 (18) [17.5]	2007-08-19	2007-11-13	2007-10-02 (by TVU)	Pregnancy outcome = normal female at term. Treatment days = 86
214 (2)	007 (29) [26.9]	2007-08-04	2008-02-11	2008-01-27 (by TVU)	Pregnancy outcome = normal male at term. Treatment days = 176
217 (3)	013 (23) [20.6]	2007-08-25	2008-04-05	2008-03-27 (by TVU)	Pregnancy outcome = normal male at term. Treatment days = 224
220 (4)	046 (22) [24.6]	2007-12-30	2008-06-21	2008-06-11 (by TVU)	Pregnancy outcome = normal female at term. Treatment days = 174
221 (5)	015 (20) [34.3]	2007-09-20	2008-07-13	2008-07-04 (by TVU)	Pregnancy outcome = normal male at term. Treatment days = 297
222 (6)	020 (22) [24.2]	2007-12-06	2008-06-26	2008-05-31 (by TVU)	Pregnancy outcome = spontaneous abortion. Treatment days = 203
241 (7)	070 (23) [26.4]	2007-11-19	2008-08-06	2008-08-12 (by TVU)	Pregnancy outcome = not provided. Treatment days = 271 EDC 6 days after last pill intake

Site	Subj. # (age) [BMI kg/m^2]	Treatment start	Treatment end	EDC	Notes
242 (8)	001 (18) [21.2]	2007-07-15	2007-11-27	2007-11-14 (by TVU)	Pregnancy outcome = normal male at term. Treatment days = 135
242 9)	013 (35) [23.6]	Not known	2007-11-28	2007-10-18 (by medical records)	Pregnancy outcome = spontaneous abortion. Treatment days = unknown
243 (10)	062 (20) [20.4]	2007-12-10	2008-11-30	2008-11-06 (by TVU)	Pregnancy outcome = not provided. Treatment days = 356
246 (11)	026 (20) [25.2]	2007-08-25	2008-01-07	2007-12-27 (by TVU)	Pregnancy outcome = normal male at term. Treatment days = 135
247 (12)	019 (32) [31.8]	2007-08-29	2007-11-26	2007-11-09 (by TVU)	Pregnancy outcome = pregnancy terminated. Treatment days = 89
255 (13)	019 (19) [20.5]	2007-12-16	2008-07-31	2008-07-22 (by TVU)	Pregnancy outcome = not provided. Treatment days = 228
257 (14)	011 (21) [20.5]	2007-11-01	2008-07-10	2008-06-05 (by TVU)	Pregnancy outcome = normal male at term. Treatment days = 217
261 (15)	012 (24) [32.3]	2007-12-06	2008-07-15	2008-06-24 (by medical records)	Pregnancy outcome = spontaneous abortion. Treatment days = 222
262 (16)	034 (28) [18.1]	2007-12-10	2008-05-08	2008-04-20 (by TVU)	Pregnancy outcome = normal female at term. Treatment days = 150
263 (17)	073 (19) [26.6]	2007-11-25	2008-11-22	2008-11-10 (by TVU)	Pregnancy outcome = spontaneous abortion. Treatment days = 363
268 (18)	002 (20) [30.3]	2007-10-14	2008-01-03	2007-12-18 (by TVU)	Pregnancy outcome = normal male at term. Treatment days = 81
Age > 35 - Within 13 Cycles – EDC while on treatment					
223	014 (40) [27.3]	2007-09-25	2007-12-18	2007-12-02 (by medical records)	Pregnancy outcome = pregnancy terminated. Treatment days = 84

TVU = transvaginal ultrasound; EDC = estimated date of conception
Source: Study Report RR-03009; pages 48-52 of 297

Medical Officer's Comment:
The following paragraph is taken from the study report regarding a reported pregnancy lacking confirmation:

> "Subject 261/009 was screened on November 5, 2007 at the age of 21 and had a screening weight of 116 lbs. She was enrolled into the study on December 7, 2007, began taking study drug on December 19, 2007, and continued until January 16, 2008; her last bleeding episode was on December 19, 2007. A urine pregnancy test done on January 17, 2008 was negative. The serum sample drawn on January 17, 2008 was beyond stability, and therefore could not be tested for pregnancy. During the subject's January 17, 2008 visit, the site noted she was taking her pills incorrectly and counseled her extensively on how to correctly take her pills. The subject's diary shows she missed pills from December 24 to 28, 2007. On February 5, 2008, the subject informed the site she was pregnant and claimed that she had seen her private physician on February 3, 2008; no ultrasound report, medical report or contact from her physician are available. The subject did not appear for her early study termination visit, which had been scheduled for February 8, 2008, and was lost to follow-up."

This reviewer considers it possible that this reported pregnancy was accurate and within the appropriate time period to qualify as a "during treatment" pregnancy. Therefore a calculation by this reviewer using 19 pregnancies for the 18-35 age range is being utilized and the Pearl Index is indicated in the boxed results immediately below.

Protocol =	***PR-00207 (Report RR-03009)***
Age group =	***18-35***
Cycles =	***1-13***
Cycles without back up contraception =	***12,297***
Number of pregnancies =	***19***
Pearl Index =	***2.01***

Pearl Index = [1300 x 19 pregnancies] divided by 12,297 cycles lacking back-up contraception

The Applicant was asked to provide life table data based on 19 pregnancies. The data in Table 9 ***reflects the Applicant's response in their Aug 3, 2010 submission***

Table 9: Life Table Analysis of Pregnancies in Study PR-00207

Relevant exposure time (days)	Number on treatment	Number pregnant	Cumulative Rate (%)
1	**1251**	**0**	**0.000**
28	**1216**	**1**	**0.081**
84	**1092**	**5**	**0.427**
140	**972**	**8**	**0.726**
196	**897**	**11**	**1.048**
252	**834**	**15**	**1.499**
308	**795**	**17**	**1.742**
364	**601**	**19**	**1.997**
371 [c]	**253**	**19**	**1.997**

C = 7 day follow-up = completed study and not pregnant within 7 days post-study
Source: Amendment 7, Aug 3, 2010; page 7 of 62

Medical Officer's Comment:
Dr. Dwyer, the FDA biostatistician, calculated the cumulative rate to be 2.0.

Pregnancies Prior to Study Treatment

The pregnancy identified prior to study treatment in Study PR-00207 is shown in Table 10.

Table 10:Study PR-00207 – Pregnancy Prior to Study Treatment

Site	Subj. (age) [BMI =kg/m^2]	Treatment start	Treatment end	EDC	Notes
244	013 (23) [35.0]	2007-10-28	2007-11-11	2007-10-12 (by TVU)	Pregnancy outcome = not provided. Treatment days = 14

TVU = transvaginal ultrasound; EDC = estimated date of conception
Source: Study Report RR-03009; page 52 of 297

Pregnancies More than 7 Days after Study Treatment

The 9 pregnancies conceived more than 7 days after study treatment are listed in Table 11.

Table 11: Study PR-00207 – Pregnancies Identified > 7 Days After the End of Treatment

Site	Subj. (age) [BMI =kg/m^2]	Treatment start	Treatment end	EDC	Notes
203 (1)	014 (36) [23.1]	2007-10-24	2008-05-08	2008-05-31 (by TVU)	Pregnancy outcome = not provided. Treatment days = 197 EDC past LTD by 23 days
207 (2)	012 (22) [25.8]	2007-11-04	2008-03-16	2008-03-31 (by TVU)	Pregnancy outcome = not provided. Treatment days = 133 EDC past LTD by 15 days
230 (3)	029 (21) [17.7]	2007-11-02	2007-12-28	2008-01-14 (by TVU)	Pregnancy outcome = Twin pregnancy (one twin with no heart beat) Treatment days = 56 EDC past LTD by 17 days
232 (4)	028 (19) [20.5]	2007-11-25	2008-03-13	2008-03-28 (by TVU)	Pregnancy outcome = Normal female at term Treatment days = 109 EDC past LTD by 15 days
246 (5)	009 (31) [31.6]	2007-08-16	2007-09-12	2007-10-08 (by TVU)	Pregnancy outcome = Normal female at term Treatment days = 27 EDC past LTD by 26 days
246 (6)	025 (18) [21.8]	2007-08-23	2007-10-17	2007-11-08 (by TVU)	Pregnancy outcome = not provided Treatment days = 55 EDC past LTD by 22 days
251 (7)	010 (26) [20.2]	2007-09-23	2007-10-22	2007-11-07 (by TVU)	Pregnancy outcome = normal male at term Treatment days = 29 EDC past LTD by 16 days
257 (8)	016 (23) [21.0]	2007-12-20	2008-02-14	2008-02-26 (by TVU)	Pregnancy outcome = normal female at term Treatment days = 56 EDC past LTD by 12 days
263 (9)	088 (22) [26.3]	2007-11-02	2008-01-31	2008-02-21 (by TVU)	Pregnancy outcome = not provided Treatment days = 90 EDC past LTD by 21 days

TVU = transvaginal ultrasound; EDC = estimated date of conception; LTD = last treatment day
Source: Study Report RR-03009; pages 52-54 of 297

5.3.1.19 Safety - Secondary Variable Results –Bleeding Parameters

Incidence of Intracyclic Bleeding/Spotting, Bleeding Only or Spotting Only by Cycle

The data are shown in Table 12.

Table 12: Study PR-00207 – Summary of Incidence of Intracyclic Bleeding and/or Spotting Bleeding Only and Spotting Only by Treatment Cycle (MITT Population, N = 1,570)

Cycle(s)	Bleeding / Spotting	Bleeding Only	Spotting Only
1	542/1462 (37.1%)	416/1462 (28.5%)	153/1462 (10.5%)
2	436/1393 (31.3%)	360/1393 (25.8%)	94/1393 (6.7%)
3	391/1322 (29.6%)	332/1322 (25.1%)	76/1322 (5.7%)
4	305/1243 (24.5%)	257/1243 (20.7%)	57/1243 (4.6%)
5	319/1206 (26.5%)	270/1206 (22.4%)	56/1206 (4.6%)
6	270/1162 (23.2%)	229/1162 (19.7%)	48/1162 (4.1%)
7	266/1134 (23.5%)	228/1134 (20.1%)	40/1134 (3.5%)
8	232/1097 (21.1%)	202/1097 (18.4%)	32/1097 (2.9%)
9	255/1062 (24.0%)	214/1062 (20.2%)	43/1062 (4.0%)
10	218/1031 (21.1%)	185/1031 (17.9%)	36/1031 (3.5%)
11	242/1021 (23.7%)	214/1021 (21.0%)	29/1021 (2.8%)
12	220/986 (22.3%)	184/986 (18.7%)	41/986 (4.2%)
13	227/964 (22.5%)	186/964 (19.3%)	36/964 (3.7%)
2-13	1028/1424 (72.2%)	918/1424 (64.5%)	377/1424 (26.5%)

Source: Study Report RR-03009; page 63 of 297

Medical Officer's Comment:
During most cycles in the first year of use, approximately 21-30% of subjects had intracyclic bleeding/spotting. The Division refers to this as unscheduled bleeding. Overall, approximately 70% of subjects will have some intracyclic bleeding/spotting sometime in the first year of use.

Number of Days of Intracyclic Bleeding and Spotting

Table 13 provides data on the number of days of intracyclic bleeding and spotting during each cycle.

Table 13: Study PR-00207 – Number of Days of Intracyclic Bleeding and / or Spotting Bleeding Only and Spotting Only During Each Cycle, Mean (SD) (MITT population, N=1,570) for 0.025 mg EE / 0.8 mg NE

Cycle(s)	Bleeding / Spotting	Bleeding Only	Spotting Only
1	1.91 (3.42)	1.36 (2.86)	0.55 (1.61)
2	1.31 (2.56)	1.04 (2.25)	0.27 (1.02)
3	1.24 (2.46)	0.95 (2.06)	0.29 (1.18)
4	0.98 (2.14)	0.78 (1.86)	0.20 (0.81)
5	1.05 (2.20)	0.87 (2.01)	0.18 (0.76)
6	0.88 (1.91)	0.71 (1.73)	0.17 (0.73)
7	0.92 (2.06)	0.77 (1.89)	0.15 (0.68)
8	0.82 (1.96)	0.68 (1.72)	0.15 (0.85)
9	0.98 (2.21)	0.82 (2.03)	0.16 (0.71)
10	0.79 (1.80)	0.66 (1.63)	0.13 (0.59)
11	0.97 (2.17)	0.84 (1.96)	0.14 (0.82)
12	0.80 (1.84)	0.67 (1.70)	0.13 (0.59)
13	0.89 (2.13)	0.76 (2.00)	0.13 (0.54)

Source: Study Report RR-03009; page 64 of 297

Medical Officer's Comment:
As shown in the previous table, the mean number of days of intracyclic bleeding/spotting decreases after the first few cycle of use.

Table 14 provides data on the incidence of withdrawal bleeding for the MITT population.

Table 14: Study PR- 00207 – Incidence of Withdrawal Bleeding (MITT Population, N=1570)

Cycle (28 days)	n/N (%) of Subjects
1	1149/1462 (78.6)
2	1038/1393 (74.5)
3	970/1322 (73.4)
4	863/1243 (69.4)
5	830/1206 (68.8)
6	789/1162 (67.9)
7	764/1134 (67.4)
8	728/1097 (66.4)
9	692/1062 (65.2)
10	633/1031 (61.4)
11	662/1021 (64.8)
12	631/986 (64.0)
13	546/964 (56.6)

Source: Study Report RR-03009; page 70 of 297

Medical Officer's Comment:
Withdrawal bleeding is also referred to as scheduled bleeding. The percentage of subjects with withdrawal bleeding decreased up through cycle 13. Therefore, at cycle 13, approximately 45% of subjects did not have withdrawal bleeding. The incidence of amenorrhea is shown in Table 15***. The numbers for amenorrhea do not match up to the incidence of withdrawal bleeding because amenorrhea was defined as the absence of both bleeding and spotting.***

Table 15: Study PR- 00207 – Incidence of Amenorrhea (MITT Population, N=1570)

Cycle (28 days)	n/N (%) of Volunteers
1	69/1462 (1.2)
2	113/1393 (8.1)
3	132/1322 (10.0)
4	137/1243 (11.0)
5	138/1206 (11.4)
6	154/1162 (13.3)
7	176/1134 (13.6)
8	169/1097 (16.0)
9	186/1062 (15.9)
10	169/1031 (18.0)
11	186/1021 (16.6)
12	182/986 (18.5)
13	177/964 (18.4)

Source: Study Report RR-03009; page 76 of 297

The Applicant was asked in an information request to provide the mean number of days of withdrawal bleeding per cycle. This is presented in Table 16***.***

Table 16: Mean Number of Days of Withdrawal Bleeding – MITT, N=1570

Cycle (28 days)	N	Mean
1	1462	3.02
2	1393	2.61
3	1322	2.26
4	1243	2.20
5	1206	2.13
6	1162	2.03
7	1134	1.84
8	1097	1.85
9	1062	1.76
10	1031	1.86
11	1021	1.60
12	986	1.71
13	964	1.77

Source: Amendment 7; Aug 3, 2010; page 35 of 62

The total number of bleeding days (intracyclic and withdrawal) are shown in Table 17.

Table 17: Total Number of Bleeding Days per Cycle, Mean (SD) – MITT, N=1570

Cycle (28 days)	Number of Days per Cycle, Mean (SD)
1	7.10 (5.26)
2	4.40 (3.19)
3	4.21 (3.17)
4	3.78 (2.75)
5	3.74 (2.81)
6	3.52 (2.51)
7	3.47 (2.67)
8	3.30 (2.56)
9	3.40 (2.67)
10	3.12 (2.29)
11	3.29 (2.69)
12	3.15 (2.52)
13	3.11 (2.68)

Source: Study Report RR-03009; page 74 of 297

Medical Officer's Comment:
Because Cycle 1 started on the first day of bleeding, the number of days is greater than succeeding cycles.

5.3.1.20 Safety – Extent of Exposure

The exposure to 0.025 mg EE / 0.8 mg NE in Study PR-00207 by cycles, partial cycles and women-years is the following:

- Number of completed 28 day cycles (all 28 pills taken) = 15,548 cycles
- Number of partially completed 28 day cycles (at least 1, but < 28 pills) = 977 cycles
- Total women-years of exposure (based on the sum of all known durations of treatment) = 1,181 women years

Medical Officer's Comment:
The Applicant provided this information in response to a Division information request (Aug, 2010). This amount of safety data is acceptable given that a combination product containing EE/NE has been well studied for over 40 years and this product contains a dosage that is less than other EE/NE products on the market.

5.3.1.21 Safety – Event Overview

The safety event overview is shown in Table 18.

Table 18: Study PR-00207 – Summary of Treatment Emergent Adverse Events in All Treated Subjects (N =1677)

Subjects	0.025 mg EE / 0.8 mg NE N = 1677 n (%)
Number of subjects with at least 1 adverse event	1062 (63.3)
Number of subjects with at least 1 serious adverse event	22 (1.3)
Number of subjects with AE leading to discontinuation	136 (8.1)

Source: Study Report RR-03009; page 78 of 297

Medical Officer's Comment:
There were 2,768 adverse events overall.

5.3.1.22 Safety – Common Adverse Events

A listing of subjects with common adverse events occurring in ≥ 2% of the subjects in Study PR-00207 is shown in Table 19.

Table 19: Study PR-00207 – Most Common Adverse Events (Occurring in at Least 2% of All Treated Subjects, N = 1677)

Adverse Event (PT)	0.025 mg EE / 0.8 mg NE N =1677 n (%)
Upper respiratory tract infection	122 (7.3)
Nasopharyngitis	121 (7.2)
Nausea	**102 (6.1)**
Sinusitis	91 (5.4)
Headache	**80 (4.8)**
Urinary tract infection	80 (4.8)
Dysmenorrhea	**66 (3.9)**
Vaginitis bacterial	58 (3.5)
Acne	**54 (3.2)**
Vulvovaginal mycotic infection	**52 (3.1)**
Vomiting	**46 (2.7)**
Bronchitis	46 (2.7)
Weight increased	**38 (2.3)**
Smear cervix abnormal	36 (2.1)
Anxiety	36 (2.1)
Fungal infection	**35 (2.1)**
Diarrhea	**34 (2.0)**
Gastroenteritis viral	34 (2.0)

Source: Study Report RR-03009; page 80 of 297

Medical Officer's Comment:
Although there is no comparator in this study, these adverse events are comparable to other COC trials. The adverse events more likely to be related to pill use have been bolded by this reviewer.

5.3.1.23 Safety – Nonfatal Serious Adverse Events (SAEs)

Table 20 provides safety data on the 22 subjects with nonfatal SAEs in Study PR-00207.

Table 20: Study PR-00207 – Nonfatal Serious Adverse Events

Site	Subject (Cumulative # of Subjects with SAEs)	Duration of Treatment at SAE onset (days)	SAE(s)	Comment
200	085 (1)	159	Viral meningitis	Recovered
		159	Headache	Recovered
209	018 (2)	233	Depression	Ongoing
		333	Suicidal ideation	Recovered
221	025 (3)	33	Flank pain	Recovered
227	008 (4)	193	Asthma	Recovered
		193	Respiratory tract infection	Recovered
231	005 (5)	123	Anxiety	Recovered
		123	Major depression	Recovered
231	018 (6)	267	Multiple fractures	Recovered
235	024 (7)	18	Chest pain (Depression)	Recovered
237	015 (8)	101	Cholecystectomy	Recovered
238	002 (9)	74	Appendicitis	Recovered
238	031 (10)	230	Angina pectoris	Recovered
		230	Hypertension	Recovered
241	007 (11)	10	Suicidal ideation	Recovered
241	058 (12)	195	Vomiting	Recovered
		195	Abdominal pain	Recovered
242	021 (13)	363	Chest pain	Recovered
243	065 (14)	220	Staph infection	Recovered
256	017 (15)	342	Intervertebral disc surgery	Recovered
259	046 (16)	126	Abdominal pain	Recovered
262	024 (17)	-9	Intervertebral disc protrusion	Recovered
263	046 (18)	370	Cervical dysplasia	Ongoing
263	056 (19)	329	Hemorrhagic diarrhea	Recovered
		330	Dehydration	Recovered
		330	Ischemic colitis	Recovered
264	013 (20)	25	Lumbar vertebral fracture	Ongoing
265	044 (21)	217	Blood pressure increased	Recovered
223	030 (22)	12 days post completion of study	Deep vein thrombosis	Recovered
255	015 (23)	Approx 3.5 weeks post study completion	Marked liver enzyme elevation (Hy's Law)	Recovered
			Cholecystitis	
			Cholecystectomy	
208	037 (24)	End of study	Mononucleosis	Ongoing
			Marked liver enzyme elevation (Hy's Law)	

Source: Study Report RR-03009; pages 85-86 and 89-95 of 297 and Amendment 7, Aug 3, 2010

Medical Officer's Comment:
Two additional serious adverse events were added by this reviewer to the preceding table based on marked liver laboratory abnormalities that qualified for Hy's Law. Additional clinical information on these 2 subjects

can be found in the laboratory section of the review (Section 5.3.1.26). Therefore there were 24 subjects with serious adverse events. Other pertinent clinical summaries for cases in the preceding table are listed below:

> "Subject 018, a 38-year-old woman at Site 209, began taking study drug in Study PR-00207 on 20 October 2007. On (b) (6), she was found pointing a gun to her chest and was admitted to her local hospital and placed on suicide watch. Her admission diagnosis was major depression and threatened suicide. She had been receiving treatment for major depression for several years. The investigator assessed the suicidal ideation as severe and unlikely related to treatment. The subject remained hospitalized until (b) (6) and was prescribed fluoxetine and discharged home in much improved condition. She was scheduled to return for electroconvulsive therapy. Her final diagnosis was major depression that was unlikely related to study drug. She remained in the study."

Although Subject 018 had a history of major depression prior to the study this reviewer cannot rule out a worsening of her condition with study drug. The progestin component of COCs is thought to be related to depression and mood changes.

> "Subject 005, a 40-year-old woman at Site 231, began taking study drug in Study PR-00207 on 15 August 2007. On (b) (6), she developed a panic attack with symptoms of sleep loss, paranoid ideation, and dry mouth. The intensity of the event was severe and the subject was hospitalized. She had a history of anxiety and had been treated with paroxetine hydrochloride in the past. She was prescribed bupropion hydrochloride as therapy for this event. The investigator characterized this event as anxiety, not related to study drug. Her hospital records showed that her diagnoses on discharge were Major Depressive Disorder and Anxiety Disorder. The subject remained in the study."

Although Subject 005 had a history of anxiety and treatment prior to the study, this reviewer cannot rule out a relation to study drug.

> "Subject 024, a 42-year-old woman at Site 235, began taking study drug in Study PR-00207 on 10 November 2007. On (b) (6), she experienced chest pain and was admitted to the hospital for evaluation. It was determined that the pain was of gastrointestinal origin and she was released the following day. Further evaluation for cardiac causes was negative. An additional diagnosis of depression was added at hospital discharge. The investigator characterized the SAE as severe

gastroesophageal reflux disease that was unlikely related to study drug. The SAE was ongoing at last report. The subject continued in the study."

Although the study drug should not be related to gastroesophageal reflux, it may have had a relationship to the subject's depression.

"Subject 015, a 45-year-old woman at Site 237, began taking study drug in Study PR-00207 on 10 October 2007. On (b) (6), she developed a sudden onset of muscle aches, headache, anorexia, nausea, and vomiting. She was seen at a local hospital and an abdominal ultrasound showed cholelithiasis and acute cholecystitis. The subject was hospitalized and underwent a laparoscopic cholecystectomy on (b) (6). She subject recovered and was discharged 2 days later. The investigator classified this SAE as severe and possibly related to study drug. The subject withdrew consent and was discontinued from the study on 20 June 2008."

Medical Officer's Comment:
This is possibly related to study drug, since COCs have been associated with cholelithiasis.

"Subject 031, a 22-year-old woman at Site 238, began taking study drug in Study PR00207 on 19 December 2007. She was reported to have been hospitalized on (b) (6) due to a hypertensive episode. The investigator's initial assessment of this SAE was that it was moderate in intensity and possibly related to study drug. A follow-up report indicated that on (b) (6), the subject complained of chest pain with radiation into the neck and numbness in her left arm. The subject was discontinued from the study on 24 September 2008 due to the angina pectoris."

Medical Officer's Comment:
In response to an information request the Applicant provided the following information on Subject 238031:

"Subject 238/031 had a history of hypertension and developed worsening of her hypertension during the study. This required adjustment of her medications. At about the same time she went to the ER of a local hospital with a complaint of chest pain, tingling, numbness of her left arm with radiation to her neck and was hospitalized for observation and evaluation. During the hospitalization it was determined that she had not had a myocardial infarction and, except for minor valvular abnormalities seen on an echocardiogram, she did not have any evidence of cardiac disease. Chest CT showed some pulmonary nodules, which had been noted previously. The plan on discharge included control of her blood pressure

and referral to a rheumatologist to assess the chest and arm pain and numbness."

This reviewer concurs with the Applicant's decision to call this adverse event chest pain, nonspecific rather than angina, which connotes coronary artery disease. Worsening of hypertension, however, could have been associated with her study drug use.

"Subject 007, a 21-year-old woman at Site 241, started taking study drug in Study PR-00207 on 29 June 2007. On (b) (6), she was hospitalized due to depression and suicidal ideation. She had a history of depression and post-traumatic stress disorder. She was prescribed an antidepressant (citalopram hydrobromide) and was discharged on (b) (6). The subject was discontinued from the study due to the SAE and remained on antidepressant therapy. The subject recovered. The investigator considered the SAE to be severe and unlikely related to study drug."

Medical Officer's Comment:
As noted before, there may be a relationship between depressive episodes and COCs.

Subject 058, a 28-year-old woman at Site 241, began taking study drug in Study PR-00207 on 31 October 2007. On (b) (6), the subject developed vomiting and abdominal pain for which she was hospitalized. She was treated symptomatically and recovered. The subject was discharged on (b) (6) with a final diagnosis of probable viral gastroenteritis. The investigator assessed these SAEs as moderate in intensity and unlikely related to study drug. Study drug was discontinued on 21 May 2008 and the subject was discontinued from the study on 3 June 2008 due to the abdominal pain.

Medical Officer's Comment:
A relationship to study drug is unlikely in this case.

Subject 021, a 33-year-old woman at Site 242, began taking study drug in Study PR-00207 on 12 September 2007. On (b) (6), she presented to her local hospital with chest pain. She was admitted for observation and diagnostic testing. Results of an ECG and other investigations were normal and the subject was discharged with a presumptive diagnosis of chest pain due to stress. The investigator assessed this SAE as mild and unlikely related to treatment. The subject remained in the study.

Medical Officer's Comment:
There does not appear to be a relationship to study drug.

Subject 046, a 22-year-old woman at Site 259, began taking study drug in Study PR-00207 on 24 December 2007. At a clinic visit on 13 May 2008, she notified the staff that she had developed abdominal pain on (b) (6) and was hospitalized. Diagnostic studies including ultrasound revealed that the subject had pelvic inflammatory disease. She was treated symptomatically with metronidazole, clindamycin, and gentamicin; recovered on 28 April 2008; and was discharged from the hospital on (b) (6). The investigator assessed the SAE as severe in intensity and not related to study drug. The subject continued in the study.

Medical Officer's Comment:
A relationship to study drug is unlikely in this case. Due to alterations in cervical mucus, COCs tend to reduce pelvic inflammatory disease.

Subject 056, a 30-year-old woman at Site 263, began taking study drug in Study PR-00207 on 14 October 2007. On (b) (6), she presented to her local hospital and complained of bloody diarrhea of one day's duration. She was admitted with presumptive diagnoses of ischemic colitis and dehydration. She was discharged the following day. The subject had been taking systemic antibiotics and prednisone for insect bites and had stopped several days before the onset of her GI symptoms. She was considered recovered and discharged the following day with a prescription for levaquin. A follow-up colonoscopy was performed on (b) (6), which showed moderate ischemic colitis in the sigmoid colon. No culture was performed for Clostridium dificile. No biopsy results were available. The investigator assessed the SAEs as severe and not related to treatment. The subject continued to take study drug and completed the study on 23 October 2008.

Medical Officer's Comment:
A relationship to study drug is unlikely in this case.

Subject 044, a 36-year-old woman at Site 265, began taking study drug in Study PR-00207 on 30 December 2007. She was reported to have been hospitalized on (b) (6), due to a hypertensive episode. Per the subject, her blood pressure at the time of admission was 148/113 mm Hg. The investigator assessed the SAE as mild and possibly related to study drug. The subject continued to receive study drug.

Medical Officer's Comment:
There is a relationship between COCs and hypertension.

Subject 030, a 36-year-old woman at Site 223, began taking study drug in Study PR-00207 on 15 November 2007 and completed the study treatment and the study on 12 November 2008. On 9 March 2009, she was seen by the investigator during a routine patient visit and revealed that on (b) (6), she had

been hospitalized for 2 days due a deep vein thrombosis (DVT) and had been started on therapy with coumadin. Her DVT had resolved by 12 January 2009. It was also noted during the 9 March 2009 visit that she was pregnant. The pregnancy was terminated due to the known teratogenicity of coumadin.

Medical Officer's Comment:
Based on the time between stopping treatment and being diagnosed with a DVT it is likely that the study drug was related.

5.3.1.24 Safety – Deaths

There were no deaths in Study PR-00207.

5.3.1.25 Safety – Discontinuations Due to Adverse Events

The adverse events leading to discontinuation are shown in Table 21.

Table 21: Study PR-00207 – Subjects with Adverse Events Leading to Discontinuation in > 1 Subject (All Treated Subjects, N =1,677)

Adverse Event -PT	N = 1,677 No. of subjects (%)
Nausea	17 (1.0)
Weight increased	14 (0.8)
Acne	13 (0.8)
Metrorrhagia	12 (0.7)
Mood altered	6 (0.4)
Hypertension	6 (0.4)
Irritability	5 (0.3)
Migraine	5 (0.3)
Libido decreased	5 (0.3)
Mood swings	5 (0.3)
Abdominal pain	4 (0.2)
Anxiety	4 (0.2)
Dysmenorrhea	4 (0.2)
Edema peripheral	3 (0.2)
Headache	3 (0.2)
Depression	3 (0.2)
Menstruation irregular	3 (0.2)
Vomiting	2 (0.1)
Dizziness	2 (0.1)
Crying	2 (0.1)

Source: Study Report RR-03009; page 88 of 297

5.3.1.26 Safety – Standard Safety Labs

The only laboratory abnormalities of concern to this reviewer are found in Table 22.

Table 22: Very Significant Laboratory Abnormalities in Study PR-00207

Site	Subject	Visit #	Lab test	Result	Normal range
208	037	8 (Final)	ALT	309 U/L	6-34
			Alk Phosph	340 U/L	31-106
			AST	263 U/L	9-34
			Bilirubin	2.6 mg/dL	0.2-1.2
			GGT	240 U/L	4-49
			LDH	626 U/L	53-234
			WBC	12.9 x 10/uL	3.8-10.7
209	005	Baseline	Triglycerides	494 mg/dL	39-176
		8 (Final)	Triglycerides	514 mg/dL	39-176
255	015	8 (Final)	ALT	509 U/L	6-34
			Alk Phosph	150 U/L	31-106
			Bilirubin	2.9 mg/dL	0.2-1.2
			GGT	673 U/L	4-49

ALT = Alanine transaminase; AST = aspartate transaminase; Alk Phosph = alkaline phosphatase; LDH = lactate dehydrogenase; GGT = gamma glutamyl transferase; WBC = white blood cell count
Source: Laboratory dataset for Study PR-00207

Medical Officer's Comment:
The Applicant was asked in an information request to provide more information on these three subjects. The following responses were provided (by Applicant Aug 3, 2010):

The abnormal liver tests for Subject 208/037 were attributed to infectious mononucleosis. There were no follow-up labs available.

The abnormal liver tests for Subject 255/015 were attributed to cholecystitis. This subject had a cholecystectomy approximately 3.5 weeks after completing the study. The liver enzymes were reported to be normal one week following the surgery. Her study COC could have been indirectly responsible for the liver lab abnormalities, because COCs are associated with gall bladder disease.

The abnormal triglycerides for Subject 209/005 were attributed by the Applicant to pre-existing, possible familial, hypertriglyceridemia. There appeared to be only a minor increase at the end of study compared to baseline. Many clinicians would probably avoid COCs in such patients due to rare but serious cases of pancreatitis developing.

5.3.1.27 Safety – Vital Signs and Weight

There were no clinically significant mean changes in vital signs during the course of the study for the All Treated Subjects population. Vital signs measurements reported as AEs by the Applicant included weight increased in 38 subjects (treatment-related in 30 subjects). Hypertension was reported as an AE in 19 subjects; in 11 of these, hypertension was considered to be treatment-related. Fourteen subjects were discontinued because of weight gain (11 treatment related) and 6 subjects (4 treatment related) were discontinued for hypertension.

Medical Officer's Comment:
Weight gain and hypertension are known adverse events associated with COCs.

5.3.2 Supportive Safety Study PR-10107 (Report RR-00309)

5.3.2.1 Study Title, Principal Investigator, Study Dates

"A Clinical Study to Evaluate the Safety of an Investigational Chewable Oral Contraceptive (0.025 mg EE / 0.8 mg NE) Following Daily Use By Human Female Subjects"

The principal investigator was Mark LeFelt, DDS.

This study ran from October 3, 2008 through December 2, 2008.

5.3.2.2 Ethics

The protocol and informed consent documents were reviewed and approved on September 16, 2008 by IntegReview Ethical Review Board in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 56. The study was carried out in accordance with Good Clinical Practice (GCP). These standards are in accordance with the International Conference on Harmonization (ICH) and the Guideline for Good Clinical Practice.

5.3.2.3 Study Sites

There was one study site – TKL Research, Inc. – Paramus, New Jersey.

5.3.2.4 Study Objectives

The **primary** objective of the study was to determine the irritation potential of a chewable oral contraceptive tablet following daily use of the active formulation for 24 days.

The **secondary** objective of this study was to assess adverse events.

5.3.2.5 Study Design

This was an open-label, uncontrolled single-center study to determine the irritation potential of a chewable oral contraceptive following daily use of the active formulation for 24 days. Subjects had an oral soft-tissue examination (OSTE) immediately before their first dose. Subjects chewed their first dose of study product under the supervision of a member of the clinical staff.

Subjects had an OSTE 30 minutes post-dose on Day 1. Subjects returned for visits on Day 3, Day 8, Day 24 and Day 28. Subjects were given an OSTE on each of these study visits.

The procedure for the OSTE was as follows:

The dentist evaluated the intra-oral soft tissues for irritation/inflammation and abrasions. The condition of the lips, buccal mucosa, labial mucosa, sublingual mucosa, gingivae, tongue, hard/soft palate, uvula and oropharynx were evaluated and recorded. Clinically significant findings were recorded as adverse events. Everyday traumatic findings (e.g., as a result of chewing or daily oral hygiene) were not reported as adverse events, unless deemed clinically significant.

The irritation/inflammation of each area was evaluated using the following scale:

0 = Normal
0.5 = Slight erythema, no edema
1 = Erythema plus slight edema
2 = Moderate erythema and/or edema (i.e., beginning of tissue breakdown or slough)
3 = Severe irritation/inflammation (i.e., definite blistering, ulceration, or epithelial slough)

The severity of any abrasions noted in each area was evaluated using the following scale:

0 = None
1 = Mild
2 = Moderate
3 = Severe

5.3.2.6 Inclusion Criteria

The inclusion criteria consisted of the following:

- Females 18 to 45 years of age;
- Good general health and a negative urine pregnancy test at Baseline;
- Willing to switch to the study product during the course of the study if they were currently using oral, intravaginal, or transdermal combination contraceptives;
- Willing to use a non-hormonal (e.g., barrier) method of contraception during the period of the clinical study, and continue that method for 1 month after stopping use of the experimental medication; and
- Could read, understand, and sign an informed consent agreement

5.3.2.7 Exclusion Criteria

The exclusion criteria consisted of the following:

- Use of injectable hormones or hormonal implants within 9 months of study entry; use of intrauterine contraception within 3 month of study entry (women who were on oral, intravaginal or transdermal combined oral contraceptives could be switched directly to study medication at the time of the study);
- Post-menopausal or perimenopausal (experiencing hot flushes, new menstrual irregularities, etc.);
- Visible disease of the oral mucosa which, in the opinion of the investigative personnel, would have interfered with the evaluation;
- Had a condition which, in the opinion of the investigative personnel, suggested a significant hazard for the subject, or which may have confounded the study results or interfered with the subject's participation in the study;
- Had any medical and/or physical findings or conditions (e.g., pelvic examination, vital signs), which, in the opinion of the investigative personnel, would place the subject at undue risk or otherwise interfere or influence the outcome of the study;

- Had clinically relevant abnormal findings on the baseline dental or gynecologic exam;

- Had a known sensitivity to oral contraceptives;

- Age 35 or older and smoked;

- Had a contraindication for the use of oral contraceptives (e.g., history of thrombophlebitis or thromboembolic disorders, known or suspected clotting disorders, cerebral vascular or coronary artery disease, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, genital bleeding of unknown cause, or a history of benign or malignant liver tumor or liver disorders);

- Had dentures, which, in the opinion of the investigative personnel, would have resulted in reduced oral contact with the investigative drug;

- Had participated in another clinical trial within 1 month prior to Screening, or received an investigational drug within the last 3 months prior to Screening. Subjects who participated in an Oral Contraceptive clinical trial, using FDA-approved active ingredients, were allowed to be enrolled 2 cycles after completing the preceding study;

- Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results; and/or

- Were females who were pregnant, planning to become pregnant during the study, or were breastfeeding.

5.3.2.8 Study Procedures

Study procedures are shown in Table 23

Table 23: Study 10107 – Study Procedures

Cycle	S	PrD	PstD Day1	Day 3	Day 8	Day 24	Day 28
Informed consent	X						
Medical history	X						
Entry criteria	X						
Urine pregnancy test		X					X
Pelvic examination	X						
Oral soft-tissue examination	X	X	X	X	X	X	X
• Irritation/inflammation							
• Abrasions							
Blood pressure / pulse	X	X		X	X	X	X
Product dispensed	X	X					
Prior / concomitant meds	X	X		X	X	X	X
Adverse events			X	X	X	X	X

S = screening; PrD = predose; PstD = postdose;
Source: Study Report RR-00309; page 20 of 477

5.3.2.9 Efficacy Measurement

Efficacy was not measured in this study (the oral exam was a safety variable).

5.3.2.10 Analysis of Safety

The following safety assessments were conducted:

- Oral soft-tissue examination (OSTE)
- Adverse events
- Medical history and assessment of entry criteria related to safety
- Pelvic examination
- Blood pressure and pulse
- Concomitant medication assessment

5.3.2.11 Disposition of Subjects

Table 24 provides data on the disposition of subjects in Study PR-10107.

Table 24: Study 10107 – Disposition of Subjects

Disposition / Reason	0.025 mg EE / 0.8 mg NE
Subjects enrolled	54 (100%)
Subjects prematurely discontinued	2 of 54 (3.7%)
• Withdrawal of consent	• 1 of 54 (1.9%)
• Loss to follow-up	• 1 of 54 (1.9%)
Completed	52 of 54 (96.3%)

Source: Study Report RR-00309; page 27 of 477

5.3.2.12 Demographics

Table 25 provides demographic data for Study PR-10107.

Table 25: Study 10107 – Demographic Data

	EV/DNG (N=54)
Mean age (years ± SD)	35.2 ± 4.4
Age range (years)	18-45
Race	
• Caucasian	44 (81.5%)
• African-American	10 (18.5%)

Source: Study Report RR-00309; page 28 of 477

5.3.2.13 Safety – Oral Evaluations

Irritation/Inflammation

The results of the oral evaluation for irritation/inflammation are shown in Table 26.

Table 26: Study 10107 – Number of Subjects with Irritation and Inflammation in Oral Region

	S	PrD	PsD	Day 3	Day 8	Day 24	Day 28
N	54	54	54	53	52	50	52
Lips	0	0	0	0	0	0	0
Buccal mucosa	0	0	0	0	0	0	0
Labial mucosa	0	0	0	0	0	0	0
Sublingual mucosa	0	0	0	0	0	0	0
Gingivae	0	0	0	0	0	0	1
Tongue	0	0	0	0	0	0	0
Hard/soft palate	0	0	0	0	0	0	0
Uvula	0	0	0	0	0	0	0
Oropharynx	0	0	0	0	0	0	0

Source: Study Report RR-00309; page 30 of 477

Medical Officer's Comment:
As seen in the table there was almost no irritation/inflammation in this study. Only one subject (Subject 020) had slight erythema (Irritation score = 0.5, slight erythema, no edema) at the Day 28 visit.

Abrasion

There were no abrasions identified in any of the subjects at all visits.

5.3.2.14 Safety - Adverse Events Summary

There were no deaths in the study. A total of 6 adverse events were reported in 5 subjects. None of the events were serious or resulted in discontinuation of study drug. These adverse events consisted of nasopharyngitis (2), cough (1), headache (1), contusion (1) and wisdom tooth extraction (1).

5.3.2.15 Safety – Vital Signs

Mean vital sign values at Screening and Baseline were within normal range and there were no changes of clinical significance during the study.

6 Review of Efficacy

Efficacy Summary

6.1 Contraceptive Indication

6.1.1 Methods

Because there is just one Phase 3 efficacy study, this section of the review will focus entirely on summary information from that study; there are no pooled findings.

The key sections from NDA 22-573 regarding contraceptive efficacy were found in:

- Clinical Overview
- PR-00207 Study Report
- Summary of Clinical Efficacy - OC
- Integrated Summary of Efficacy - OC

6.1.2 Demographics

There were no clinical concerns about the demographics in the pivotal Phase 3 contraceptive trial PR-00207). Adequate numbers of non-Caucasians were

studied, in addition to women over 35 years of age. Full details are provided in Section 5.3.1.16.

6.1.3 Subject Disposition

Of the 1,677 subjects who received study medication in pivotal Study PR 00207, approximately 40% prematurely discontinued from the study, with 16% lost to follow-up. These percentages are comparable to other COC Phase 3 trials. Full details of the disposition of subjects in Study 00207 are found in Section 5.3.1.14.

6.1.4 Analysis of Primary Endpoint

The Applicant provided adequate pregnancy testing in Study PR 00207 and excluded cycles where back-up contraception was used. The Pearl Index of 2.01 based on 19 pregnancies in the 18-35 age group is acceptable from an efficacy standpoint.

6.1.5 Analysis of Secondary Endpoints

The summary conclusions from Applicant's secondary endpoints of intracyclic bleeding and overall safety are discussed in the safety section (Section 7.3)

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Components of NDA 22-273 Used to Evaluate Safety

The key sections from NDA 22-273 regarding safety were found in:

- Clinical Overview
- Summary of Clinical Safety
- PR-00207 Study Report
- PR-10107 Study Report
- 4-month safety update

7.1.2 Categorization of Adverse Events

AEs were monitored throughout the clinical studies, and all reported AEs were included in the safety analyses. AEs were coded using the Medical Dictionary of Regulatory Authorities (MedDRA). Datasets included System Organ Class (SOC), Lowest Level Term (LLT) and Preferred Term (PT).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall exposure to 0.025 mg EE / 0.8 mg NE in the pivotal study PR-00207 was adequate. There were over 15,000 completed 28 day cycles in a combination product containing mid-level dosages of drugs that have been marketed in the U.S. for over 40 years (ethinyl estradiol and norethindrone). In regard to duration of use, 746 subjects completed 360 days of treatment with the study drug.

7.2.2 Explorations for Dose Response

There were no Phase 2 dosing studies performed. There is over 40 years experience in dosing ethinyl estradiol and norethindrone.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable for this submission.

7.2.4 Routine Clinical Testing

Routing clinical testing did not identify any new safety concerns.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4 and the clinical pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The most important adverse events when considering the safety of COCs is that of venous and arterial thromboembolic events. There was 1 deep vein thrombosis case identified in pivotal Study PR-00207. It is not uncommon to see 1-2 thromboembolic adverse events in comparable size COC studies.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the clinical studies for this product.

7.3.2 Nonfatal Serious Adverse Events

This reviewer identified 9 subjects with serious adverse events that could possibly have been related to study drug – depression and/or suicidal ideation (4), cholecystitis and/or cholecystectomy (2), deep vein thrombosis (1), and hypertension (2). These serious adverse events have been previously reported in association with COCs. There are no new safety signals.

7.3.3 Discontinuations Due to Adverse Events

Of 1,677 subjects who took study medication, 143 discontinued due to an adverse event (8.5%). The most frequent adverse reactions leading to discontinuation were nausea (1.0%), weight increase (0.8%), acne (0.8%), metrorrhagia (0.7%), altered mood (0.4%), hypertension (0.4%), irritability (0.3%), migraine (0.3%), decreased libido (0.3%) and mood swings (0.3%).

7.3.4 Assessment of Bleeding

In the first cycle of use, 37% of subjects taking 0.025 mg EE / 0.8 mg NE in pivotal Study PR-00207 had intracyclic (unscheduled) bleeding/spotting. From Cycle 2-13, the percent of subjects with intracyclic bleeding/spotting ranged from 21-31% per cycle.

The mean number of days of intracyclic (unscheduled) bleeding/spotting was 1.91 in the first cycle of use and ranged from 0.8 – 1.31 in cycles 2-13.

The incidence of withdrawal (scheduled) bleeding was 79% in the first cycle. The incidence decreased with duration of use and was found to be 57% in cycle 13.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common drug-related adverse events (relationship to treatment assessed by this reviewer) for this product in the pivotal Phase 3 trial (PR-00207) with rates ≥ 2.0% were nausea (6.1%), headache (4.8%), dysmenorrhea (3.9%), bacterial vaginitis (3.5%), acne (3.2%), vulvovaginal mycotic infection (3.1%), vomiting (2.7%), increased weight (2.3%), anxiety (2.1%), fungal infection (2.1%) and diarrhea (2.0%).

7.4.2 Laboratory Findings

The only unusual laboratory findings were the two Hy's Law cases described in Section 5.3.1.26. The study drug was not related to the mononucleosis case but

could have been indirectly related in the case with cholecystitis and subsequent abnormalities in liver function tests.

7.4.3 Vital Signs / Body Weight

There were no safety concerns related to vital signs or body weight in the pivotal Phase 3 trial.

7.4.4 Electrocardiograms (ECGs)

Electrocardiocardiograms were not performed in the pivotal Phase 3 trial and are not required for this well-characterized combination drug product.

7.4.5 Special Safety Studies/Clinical Trials

The only special safety studied requested was that of an irritation study for this chewable product. There was no evidence of any safety concerns for the oral cavity based on this study (PR-10107).

7.4.6 Immunogenicity

Not applicable for this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were no dose-dependent safety findings, as only a single dose was studied.

7.5.2 Time Dependency for Adverse Events

There were no significant time-dependent safety findings.

7.5.3 Drug-Demographic Interactions

The drug-demographic interactions with BMI were previously discussed in Section 4.5. The biostatistician also evaluated race but no conclusion was drawn due to the small sample sizes.

7.5.4 Drug-Disease Interactions

There was no disease studied in the trials for this product (contraceptive study in healthy women).

7.5.5 Drug-Drug Interactions

See Section 4.4 and the clinical pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See Section 4.3 and the preclinical review.

7.6.2 Human Reproduction and Pregnancy Data

See Section 4.3 and the preclinical review

7.6.3 Pediatrics and Assessment of Effects on Growth

The product, 0.025 mg EE / 0.8 mg NE, is not intended for use by premenarchal females. The Pediatric Review Committee (PeRC) agreed to the Applicant's requested partial waiver/extrapolation to postmenarchal adolescents.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant did not have any reports of deleterious effect from overdose. Symptoms that would probably occur with overdose include nausea and possibly abnormal uterine bleeding. The drug abuse potential for COCs is very low. The primary withdrawal effect is physiologic withdrawal bleeding.

7.7 4-Month Safety Update

The 4-Month Safety Update was received March 26, 2010 as submission #002. There were no nonclinical or clinical studies conducted at the time of the submission and new clinical or nonclinical studies have been initiated. 0.025 mg EE / 0.8 mg NE is not marketed in any country. There is no new significant safety information from nonclinical or clinical scientific literature for ethinyl estradiol and norethindrone which would impact the approval of this product or labeling of this product.

7.7.1 Ongoing Studies

There are no ongoing studies of this product.

8 Postmarket Experience

There is no postmarketing experience with this dosage of ethinyl estradiol and norethindrone. There is extensive postmarketing experience with higher and lower dosage combinations. The Division has not received any new significant safety information from these other EE/NE products that would impact the approval of this application.

9 Appendices

9.1 Labeling Recommendations

This reviewer's recommendations regarding labeling include the following key points:

- The clinical section of the label should report a Pearl Index based on 19 pregnancies (PI= 2.01) (b) (4).
- Instructions for use should advise women to begin 0.025 mg EE / 0.8 mg NE on the first day of menstrual bleeding (b) (4)
- Instructions for switching from another combination hormonal contraceptive should be similar to that proposed in the pivotal trial.

9.2 Advisory Committee Meeting

An advisory committee meeting was not required. The combination products (ethinyl estradiol and norethindrone) are well-characterized in regard to efficacy and safety and have been marketed for over 40 years.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GERALD D WILLETT
10/04/2010

LISA M SOULE
10/06/2010

I concur with Dr. Willett's conclusions and recommendation that NDA 22-573 be approved for the indication of prevention of pregnancy.